

Evaluation of changes in myocardial perfusion and function on exercise in patients with coronary artery disease by gated MIBI scintigraphy

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Abstract

Objective—To investigate the ability of gated methoxy-isobutylisonitrile (MIBI) scintigraphy to measure changes in myocardial function as well as perfusion with exercise.

Setting—Regional cardiothoracic centre.

Patients—43 presenting with chest pain, 28 with coronary artery disease on angiography, and 15 with normal coronary arteriograms.

Results—Gated perfusion images showed an improvement in detecting regions with stenosed arteries compared with non-gated images (38/55 *v* 31/55, $p \leq 0.01$). Functional analysis showed an increase in fractional shortening of 4.11% in subjects with normal coronary arteries, whereas in those with coronary disease a fall of 0.57% was found ($p \leq 0.01$). Both perfusion and function imaging showed an improved sensitivity compared with standard exercise testing ($p \leq 0.01$). When both function and perfusion imaging were analysed all patients with coronary disease were detected. There was agreement in abnormal regions in 33/55 territories supplied by a stenosed artery. Combined perfusion and function detected 49/55 (89%) of abnormal regions, thus improving the overall sensitivity from 38/55 (69%) by perfusion imaging alone ($p \leq 0.01$).

Conclusions—Gated methoxy-isobutylisonitrile scintigraphy can successfully evaluate perfusion and function on exercise, so improving the diagnostic usefulness of this agent.

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Nuclear techniques have enabled the assessment of myocardial perfusion and regional and global cardiac function to determine the site, extent, and severity of coronary artery disease. Exercise myocardial perfusion imaging¹ and radionuclide ventriculography² have provided useful information about the functional significance of coronary artery stenoses. Some workers have added the results of these approaches to produce a highly sensitive method of detecting coronary artery disease.³⁻⁵ Moreover, assessment of ejection fraction with exercise has also been shown to be a most useful predictor of prognosis in coronary artery disease.^{6,7}

Methoxy-isobutylisonitrile is a myocardial

imaging agent with characteristics that have allowed evaluation of both perfusion and function. Both first pass ventriculography⁸ and gated imaging⁹ are reliable. We have evaluated the use of gated methoxy-isobutylisonitrile scintigraphy, and compared it with coronary angiography, to assess abnormalities in perfusion and regional wall motion with exercise for the detection and location of coronary artery disease.

Patients and methods

PATIENTS

Patients were recruited from referrals to the regional cardiothoracic centre. Entry criteria were chest pain with stable symptoms, New York Heart Association grades I and II, with no evidence of full thickness myocardial infarction on the electrocardiograph. Exclusions were severe symptoms, significant valvular or congenital heart disease and women of child bearing potential. All current medication was continued during investigations except for β blockers that were discontinued for 48 hours before exercise testing.

We studied 43 patients (aged 31-75 (13 women and 30 men).

All patients gave written informed consent to the study and approval of the local ethics committee was obtained.

CORONARY ANGIOGRAPHY

Selective coronary angiography was performed by the Judkins technique with multiple views and was reported by two experienced observers. A significant stenosis was classified as 50% diameter loss or 70% cross sectional area loss in a major vessel supplying more than 20% of the myocardium.

These patients had radionuclide imaging within one month of angiography. Subjects were excluded if a significant cardiac event had occurred—that is, myocardial infarction or unstable angina or if there had been a noticeable deterioration in their symptoms between angiography and radionuclide investigations.

EXERCISE PROTOCOL

Subjects exercised on a bicycle ergometer in the upright position. During exercise continuous electrocardiographic monitoring was performed. A 12 lead electrocardiogram and blood pressure were recorded every three minutes during the test, at the end of the test, and every three minutes during recovery.

The test was ended by symptoms, 3 mm

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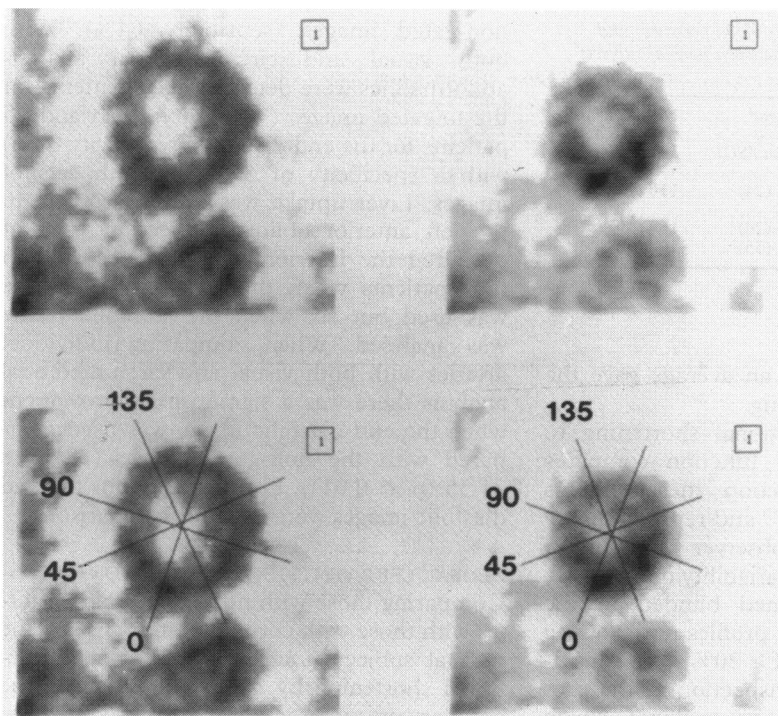


Figure 1 (Top) End diastolic and end systolic frames showing myocardial motion; (bottom) the same images with the four myocardial axes superimposed.

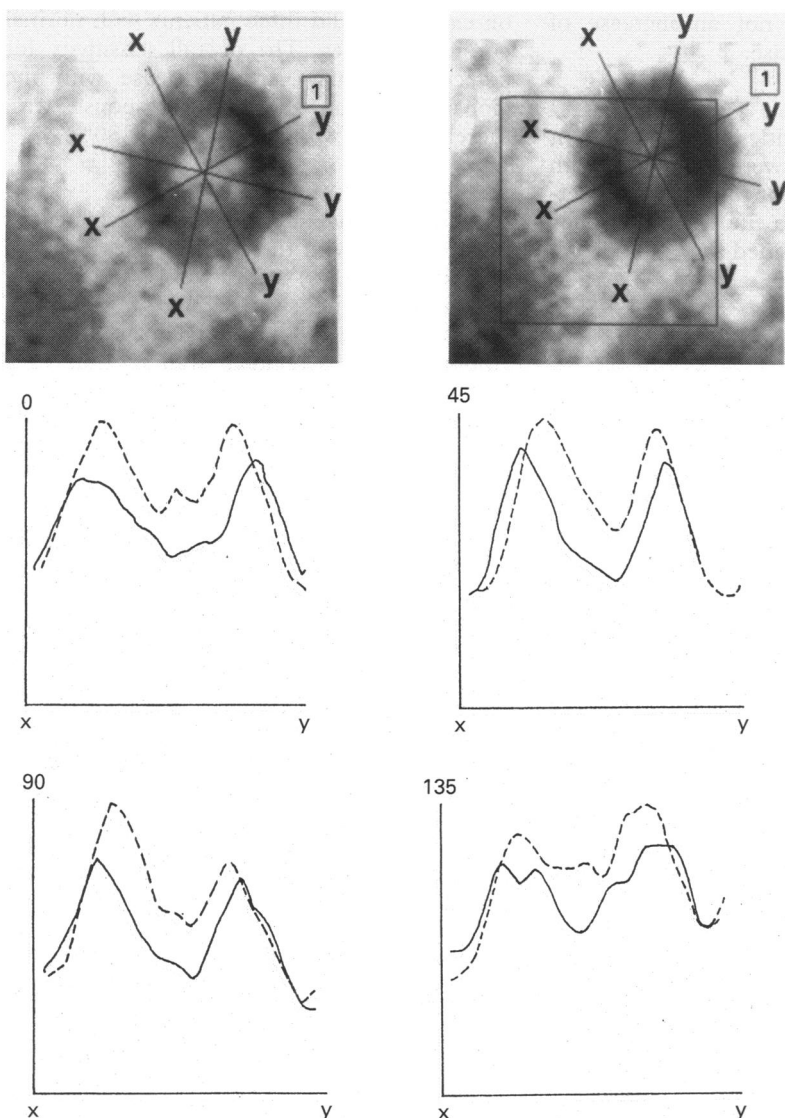


Figure 2 (Top) End diastolic and end systolic frames with the myocardial profile graphs generated by computer; (bottom) the solid line represents diastole and the dotted line systole. Contraction is seen as the peaks moving together.

horizontal ST segment depression, progressive fall in systolic blood pressure of >20 mm Hg, ST segment elevation, or arrhythmia. A positive test was defined as >1.5 mm horizontal or down sloping ST segment depression in three successive complexes. At peak exercise technetium-99m methoxyisobutylisnitrile (500 MBq) were injected intravenously and images were acquired one hour later. Rest images were taken the next day with an injection of 1000 MBq methoxyisobutylisnitrile. Images were again taken one hour later.

IMAGING PROTOCOL

Sixteen frame, gated images were taken on a single crystal mobile gamma camera with a parallel hole, low energy all purpose collimator. Data was stored on computer. Three standard projections were used left anterior oblique 40°, anterior, and left anterior oblique 70°. Non-gated images were made by summing all the 16 frames and an end diastolic image by summing frames 1 and 16.

ANALYSIS OF PERFUSION SCANS

Summed 16 frame and end diastolic images were visually assessed blind by two observers. Defects scored according to site, severity (0, normal; 1, mildly abnormal; 2, considerably abnormal), and reversibility. These images were also analysed with circumferential analysis of 10° segments to produce count graphs comparing exercise and rest. Quantitative analysis was defined as abnormal if there was <70% uptake in any region, compared with 100% in the region of highest activity. Reversibility was defined as a relative increase of 20% from rest to exercise in any abnormal region.

METHOXY-ISOBUTYLISONITRILE FUNCTION IMAGING

After the rest perfusion scan the patient again sat upright on the bicycle ergometer with the camera angled in the left anterior oblique 40° projection. A rest gated image was then obtained. The patient then exercised with the same protocol as before and gated images were taken during the last 2.5 minutes of each stage.

ANALYSIS OF METHOXY-ISOBUTYLISONITRILE FUNCTION SCANS

A computer program was devised to measure fractional shortening with count profile graphs in four axes at 0°, 45°, 90°, and 135°. The number of pixels between count peaks (pixel distance) at end diastole minus the pixel distance at end systole (ES) divided by the pixel distance at end diastole (ED) giving a figure for the fractional shortening (FS) along that particular axis.

$$FS = \frac{\text{pixel distance ED} - \text{pixel distance ES}}{\text{pixel distance ED}}$$

End diastolic and end systolic frames were selected and the profiles superimposed over them (fig 1). The computer then generated systolic and diastolic profiles along each axis (fig 2). The fractional shortening in each axis

Comparison of heart rate, systolic blood pressure, and double product at peak exercise between normal subjects and those with coronary disease

	Normal subjects Mean (SD)	Patients with coronary disease Mean (SD)
Heart rate (beats/min)	133 (24)	116 (28)
Systolic blood pressure (mm Hg)	178 (20)	166 (19)
Double product	238 (55)*	194 (58)

*p < 0.02. Values are mean (SD).

was then displayed and an average gave the global fractional shortening.

This method of fractional shortening to evaluate left ventricular function compares well with ejection fraction measurements from blood pool studies,¹⁰ and reproducibility studies showed an interobserver variability of <7% and intraobserver variability of <5%.

Analysis was performed blinded to the results of other tests and profiles not showing a fractional shortening of > 20% were considered abnormal. Visual inspection of the profiles made it possible to evaluate which myocardial regions of the profiles were responsible for the abnormal contraction. Exercise fractional shortening was defined as abnormal if there was not an increase of >2.5% from rest to exercise.

STATISTICAL ANALYSIS

Sensitivities and specificities for the different methods of assessment were compared with McNemar's test. Different responses to exercise were compared with the Mann-Whitney test. Significance was defined as p < 0.05.

Results

CORONARY ANGIOGRAPHY

Twenty eight patients had appreciable coronary artery disease; eight had three vessel, 11 had two vessel, and nine had single vessel disease. Fifteen patients had normal coronary arteriograms.

Angiography detected 55 abnormal arteries; 20 significant left anterior descending artery, 14 circumflex artery, and 21 right coronary artery lesions.

PERFUSION IMAGING

Abnormalities were detected visually in the perfusion scan in 18 of 28 patients with coronary artery disease with both the gated and

non-gated images (sensitivity 64%). With both visual and circumferential analysis abnormalities were detected in 22 patients for the ungated images (sensitivity 78%) and 25 patients for the end diastolic (sensitivity 89%) with a specificity of 57% for both sets of images. Liver uptake was only a problem in the left anterior oblique projection when it obscured the inferior wall; this occurred in four patients when the end diastolic frame was used but six when the summed frame was analysed. When comparing individual arteries with both visual and circumferential analysis there was a significant improvement when the end diastolic image was used compared with the non-gated image (38/55 v 31/55 (p ≤ 0.01)). For these reasons the end diastolic images were used for comparison.

GLOBAL LEFT VENTRICULAR FUNCTION

Comparing those with normal coronary arteries with those with coronary artery disease the normal subjects increased their global fractional shortening by 4.11% on exercise, the coronary artery disease group showed a fall in fractional shortening of 0.57% (p ≤ 0.01). Twenty patients with coronary disease, did not show an increased fractional shortening on exercise as did three patients with normal coronary arteries. The overall sensitivity for detecting coronary artery disease with the global fractional shortening response was, therefore, 71% with a specificity of 80%.

REGIONAL WALL MOTION

Region fractional shortening was detected all eight patients with three vessel disease, 10 of 11 patients (91%) with two vessel disease, and abnormalities were found in seven of nine patients (78%) with single vessel disease. Abnormalities in regional wall motion were also found in six of 15 patients (40%) with normal coronary arteries by the fractional shortening method. The sensitivity of regional fractional shortening, therefore, was 89% with a specificity of 60%.

COMPARISON OF NON-INVASIVE TESTS

The maximum work load achieved, as assessed by the double product of heart rate and systolic blood pressure, was significantly higher in the normal subjects than those with coronary disease (table). Sixteen of 28 patients with coronary artery disease had a positive exercise test (sensitivity 57%) (seven of eight patients with three vessel disease, six of eleven patients with two vessel, and four of nine patients with single vessel disease). This compares with methoxy-isobutylisocyanide perfusion imaging with an overall sensitivity of 89% (25/28) and methoxy-isobutylisocyanide function imaging with a sensitivity of 89%. This showed a significant improvement in sensitivity with both perfusion and function imaging over electrocardiographic exercise testing (p ≤ 0.01).

The combination of myocardial perfusion and function imaging identified all the patients with coronary artery disease with a specificity of 53% (fig 3).

Figure 3 Relative sensitivity, specificity, and predictive accuracy for coronary artery disease of electrocardiograph (ECG) stress testing, methoxy-isobutylisocyanide perfusion imaging (PERF), methoxy-isobutylisocyanide regional wall motion evaluation (RWM), and combined methoxy-isobutylisocyanide assessment.

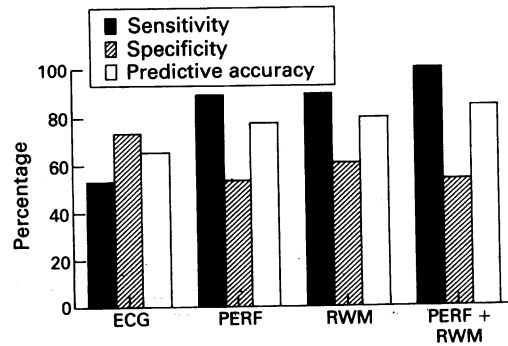
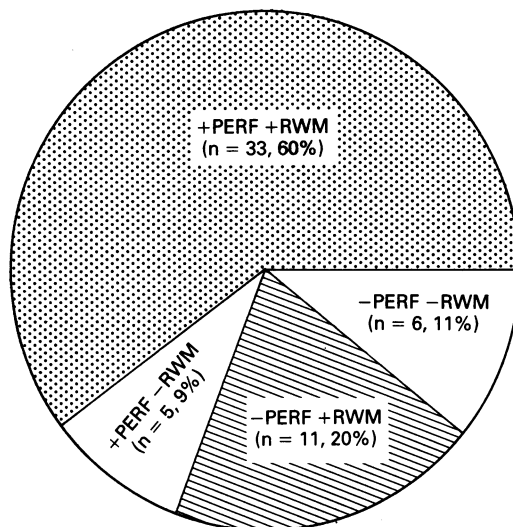


Figure 4 Comparison of methoxy-isobutylisocitrate techniques in the 55 regions supplied by a stenosed coronary artery.

Abbreviations as for fig 3; +, positive; -, negative.



Forty four of the 55 regions supplied by the abnormal arteries were identified by analysis of new regional wall motion abnormalities on exercise and 38 of the 55 by abnormalities in exercise perfusion (NS). There was agreement in 33 regions having abnormalities in perfusion and function. The addition of regional wall motion abnormalities on exercise to perfusion defects found increased the abnormal regions detected by methoxy-isobutylisocitrate from 38 to 49 ($p \leq 0.01$, fig 4).

There were five regions with normal regional wall motion but perfusion defects on exercise; one in the left anterior descending region, one in the circumflex, and three in the right coronary artery. Eleven regions had normal perfusion but exercise induced wall motion abnormalities; four in the left anterior descending region, five in the circumflex, and two in the right coronary artery.

Discussion

Experimental studies have shown a correlation between coronary artery stenosis and myocardial contraction with dysfunction occurring before electrocardiographic abnormalities.¹¹ Bodenheimer *et al* showed a close correlation between severity of coronary stenosis, decreased myocardial perfusion, and contraction in humans.¹² Glyceryl trinitrate contrast ventriculography showed reversible wall motion abnormalities in most patients with exercise induced perfusion defects. A similar correlation has been found between exercise induced abnormalities of regional wall motion and perfusion defects. Johnstone *et al* found regional wall motion abnormalities in 21 of 24 patients with a defect identified by thallium imaging on exercise,⁵ and similar results have been found by other workers.^{4,13}

Improved sensitivity for detecting coronary artery disease has been shown by abnormalities of exercise function compared with perfusion imaging.^{4,5} Single photon emission computerised tomography perfusion imaging, however, has been suggested to be the most

sensitive method of detecting coronary artery disease in patients with an equivocal electrocardiographic stress test,¹⁴ but this is not available in all centres.

The combination of perfusion and function has been shown to improve sensitivity over planar perfusion imaging alone. Caldwell *et al* showed 100% sensitivity with a 56% specificity⁴ and Bodenheimer and coworkers 96% sensitivity and 58% specificity with both perfusion and function imaging.³ The low specificity in these studies contrasts with work by Jengo *et al* who, despite showing a high sensitivity (98%) also showed a high degree of specificity (94%)¹³ and Johnstone *et al* with a sensitivity of 92% and specificity of 100%.⁵ These differences may represent a contrast in patient selection between normal controls and a control group of patients with chest pain and normal coronary arteries and to different interpretation of abnormalities of regional wall motion.

Because of a low photon energy, gated thallium scintigraphy would not allow adequate count statistics for quantitative analysis. The introduction of technetium ligands has. This study of combined methoxy-isobutylisocitrate perfusion and function imaging has shown a correlation between regional wall motion abnormalities found by regional fractional shortening measurements and perfusion defects induced by exercise similar to previous studies. Of the 38 regions with perfusion abnormalities 33 regions had abnormalities of regional wall motion.

Fractional shortening responses indicated a greater number of abnormal regions than perfusion imaging. Forty four of 55 regions supplied by an artery with a significant stenosis had regional wall motion abnormalities and 38 of 55 had exercise induced perfusion defects but this did not reach significance. The improvement in detection of coronary artery disease with wall motion analysis was in the territories of the left anterior descending and left circumflex arteries. The improvement in detection of a significant circumflex lesion by regional dysfunction has been noted before¹⁵ and combined imaging may be a particularly useful assessment of this region. There was also an improved sensitivity (89%) in detecting coronary artery disease, with both perfusion and function imaging compared with standard exercise testing, only 16 of 28 patients showed a positive electrocardiogram during stress (sensitivity 59%).

The overall detection rate for patients with coronary artery disease was 100%. This was associated with a low specificity 53%. These results are similar to some of the other series of combined perfusion and function imaging already discussed. The sensitivity of the perfusion imaging compares well with other studies of planar imaging,¹⁶ and whereas a low specificity was also found it must be noted that four subjects in the control group of normal or trivial coronary artery disease on angiography had abnormalities in all of their non-invasive tests and may represent syndrome X.¹⁷ The specificities rise significantly

to 73% if the results of these subjects were excluded from specificity calculations.

Bodenheimer *et al* also showed an improvement in detection of single vessel disease from 11% with the electrocardiogram alone to 44% with thallium imaging and 56% with regional wall motion abnormalities.³ We have shown a good detection rate for single vessel disease by evaluating regional wall motions by gated scintigraphy with an abnormality in all but one patient, with all patients having single vessel disease detected by combined imaging. This may be important for the assessment of patients undergoing coronary angioplasty as many have single vessel disease.

Despite this low specificity combined perfusion and function imaging could be performed as a screening test before coronary angiography in patients with chest pain. In this study population, 53% of the patients with normal coronary arteries—that is, 19% of the whole patient group—need not have been investigated with coronary angiography on the grounds of normal combined imaging.

Not only does the addition of myocardial function imaging improve the detection rate and accuracy of methoxy-isobutylisnitrile imaging but it may be important for estimation of prognosis in coronary artery disease and may indicate jeopardised myocardium.

Previous studies have shown a correlation between exercise function and subsequent cardiac events in coronary artery disease even in those without previous infarction,^{6,7} with the functional information from radionuclide angiography providing information that supplements coronary angiography.¹⁸ As well as an increased number of cardiac events, survival has been shown to be poorer with poor left ventricular function with exercise,¹⁹ but patients with a greater number of exercise induced left ventricular dysfunctions also have a greater benefit from bypass surgery.²⁰ Gated methoxy-isobutylisnitrile scintigraphy, by evaluating function and perfusion may, therefore, be useful in the assessment of prognosis and decision making before surgery as well as in the diagnosis.

Massie *et al* used combined perfusion and function imaging to demonstrate regions with asynergy at rest and exercise induced perfusion defects that, after revascularisation, regained normal contraction.²¹ Methoxy-isobutylisnitrile would, therefore, be an ideal agent to assess jeopardised myocardium as perfusion and function could be evaluated simultaneously. Studies are underway with gated imaging to evaluate the changes in perfusion and function after revascularisation.

A limitation of the technique of measuring myocardial function is that contraction cannot be evaluated if there is no uptake in a particular region, as with a previous full thickness myocardial infarction, although other regions can be assessed with the other profile axes.

In conclusion, gated methoxy-isobutylisnitrile scintigraphy provides a sensitive detector of coronary artery disease that may also provide prognostic information in these

patients and allow evaluation of jeopardised myocardium and adequacy of revascularisation without the need for coronary angiography in some patients.

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